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## ALTERED FRACTAL AND IRREGULAR HEART RATE BEHAVIOR IN SICK FETUSES

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The purpose of this study was to show that abnormal fractal correlation and irregularity of heart rate behavior were altered in intrauterine growth restricted fetuses (IUGR group) and fetuses whose mothers had maternal pregnancy induced hypertension (PIH group). We analyzed fetal heart rate data of 5000 points in normal ( $n=98$ ), IUGR ( $n=45$ ), and PIH ( $n=46$ ) fetuses, with their gestational ages  $> 38$  weeks and without any perinatal complication. We calculate approximate entropy for the quantifying irregularity, and short-range ( $\leq 80$  beats,  $\alpha_1$ ) and long-range ( $>80$  beats,  $\alpha_2$ ) fractal scaling exponent for quantifying the fractal correlation properties. We also performed spectral analysis. In the IUGR group, statistical, the spectral measures,  $\alpha_2$ , and  $\alpha_2/\alpha_1$  were significantly higher and the approximate entropy was significantly lower than in the normal group. In the PIH group,  $\alpha_1$  was significantly lower, and  $\alpha_2$  and  $\alpha_2/\alpha_1$  were significantly higher. The fetuses associated with either IUGR or PIH, although they are not severely compromised, showed abnormal fractal and/or irregular heart rate behavior.

### 1. Introduction

Antenatal fetal heart rate variability recordings have been widely used to evaluate fetal well-being.<sup>1</sup> However, the conventional indices of heart rate variability such as mean, variance, short-term and long-term variability have shown limitations<sup>2-3</sup> in providing information about the cardiovascular dynamics of healthy or diseased fetuses. Recently, newly developed nonlinear dynamical analysis of heart rate variability<sup>4-6</sup> makes possible the uncovering of abnormal heart rate behaviors that are not apparent from using conventional measures. This technique is actively used in early detection of cardiovascular morbidity and prediction of mortality.<sup>7-9</sup> However, the application to find abnormal behavior of heart rates in sick fetuses was limited.

Of the new techniques, fractal correlation and irregularity measures of heart rate behavior arouse much interest.<sup>8,10-11</sup> The fractal measure quantifies the temporal correlation of each heart rate value with the previous one on short- and long-range scales, and thereby, smoothness or roughness of the landscape in the heart rate time series on each scale.<sup>12</sup>

The aim of present study was to test whether uncomplicated fetuses associated with intrauterine growth restriction (IUGR) and pregnancy induced hypertension (PIH), which are the most frequently encountered fetal sicknesses, had abnormalities in fractal and irregular heart rate behavior.

## 2. Methods

### 2.1. Subjects

Among the pregnant women who had visited the outpatient obstetric clinic of Hanyang University Hospital, 98 uncomplicated cases of pregnant women and 45 cases of pregnant women whose fetuses were suspected of IUGR and were confirmed after delivery were, included in this study. We also included the 46 fetuses whose mothers had severe PIH. Severe PIH was defined when one or more of the following criteria were satisfied: Blood pressure  $\geq 160/110$  mmHg, proteinuria  $\geq 2+$  on reagent strip, oliguria  $< 400\text{mL}/24$  hours, elevated liver enzymes, platelet  $< 100,000/\text{mm}^3$ , and pulmonary edema. All were single pregnancies, with gestational ages between 39 and 42 weeks which were calculated using the date of the last menstrual period and early ultrasound measures. All births were without any major malformations, chromosomal anomalies, and perinatal complication. Using growth standards of Brenner et al.<sup>13</sup>, birth weights of infants were determined against gestational ages. Infants with birth weights below the 10th percentile were regarded as IUGR. At the time of recording, pregnant women in labor or taking drugs, including smoking, which can affect the fetal heart rate variability, were excluded.

### 2.2. Data collection

All subjects were in a semirecumbent position for a minimum of 10 minutes before data collection. Fetal heart rate tracings were recorded for more than 40 minutes using a Corometrics 115 (Corometrics, Model 115, USA) external fetal monitor. The recorded data were sampled into a personal computer with a digital serial interface. Whenever missing data were found, they were recorded as zero. Above 10 percent signal loss in the entire data have been excluded. When the off-line fetal heart rate data of zero (missing data) or below 30 beats per minute or above 200 beats per minute were encountered, they were removed. We selected 5000 points-data which corresponded to about 30 minutes of recording during which fetal movements were included.

### 2.3. Power spectral analysis

Power spectral analysis was performed by classical fast Fourier transformation.<sup>14</sup> We calculated low-, and high-frequency power by integrating the power spectral density curve at area between 0.03 and 0.15 Hz, and 0.15 and 0.4 Hz, respectively.<sup>11</sup>

### 2.4. Detrended fluctuation analysis

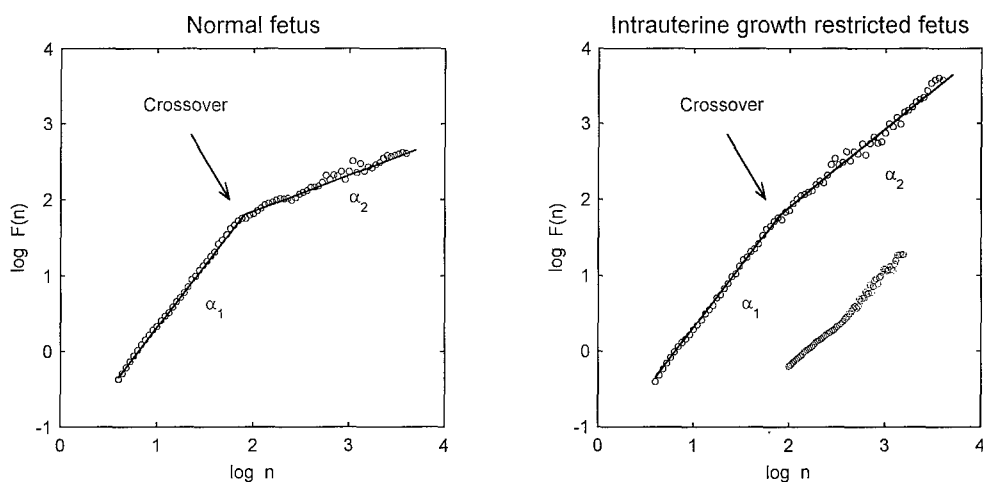
To quantify the fractal correlation behavior, we employed the detrended fluctuation analysis,<sup>4,8,15</sup> which is a modification of classical root-mean square analysis of a random walk. The heart rate time series (length  $N=5000$ ) was first integrated,

$$y(k) = \sum_{i=1}^k [x(i) - x_{ave}]$$

where  $x(i)$  is the  $i$ th heart rate and  $x_{ave}$  is the average heart rate. Next the integrated time series was divided into boxes of equal length,  $n$ . In each box of length  $n$ , a least squares line was fit to the data. The  $y$ -coordinate of the straight-line segments is denoted by  $y_n(k)$ . Next, we detrended the integrated time series,  $y(k)$ , by subtracting the local trend,  $y_n(k)$ , in each box. The root-mean-square fluctuation of this integrated and detrended time series is calculated by

$$F(n) = \sqrt{\frac{1}{N} \sum_{k=1}^N [y(k) - y_n(k)]^2}$$

This computation was repeated over all time scales (box sizes) to provide a relationship between  $F(n)$  and  $n$ . Typically  $F(n)$  will increase with  $n$ . A linear relationship on a double-log graph indicates the presence of scaling. The slope of the line relating  $\log F(n)$  to  $\log(n)$  determines the fractal scaling exponent. However, in most of the fetuses' heart rate time series, we found that log-log plot was not strictly linear but rather consisted of two distinct linear regions of different slopes separating at a break point near 80 beats (Fig.1, Crossover point).



**Figure 1.** Plots of  $\log F(n)$  vs  $\log(n)$  (see text) in a normal and a growth restricted fetus aged 40 weeks of gestation. For both fetuses, detrended fluctuation analysis curves are approximated linear over two regions, with a slope  $\alpha_1$  for small values of  $n$  ( $\leq 80$  heartbeats, short-range fractal scaling exponent) and  $\alpha_2$  for large values of  $n$  ( $> 80$  heartbeats, long-range scaling exponent), resulting in apparent crossover phenomena. Note  $\alpha_1$  is similar in both fetuses (1.253 vs 1.248). However,  $\alpha_2$  is significantly higher in the growth restricted fetus (1.092 vs 0.652). Arrows indicate crossover points.

Therefore, fractal correlation of heart rate was defined separately for short-range ( $\leq 80$  beats, short-range fractal scaling exponent,  $\alpha_1$ ) and long-range ( $> 80$  beats, long-range fractal scaling exponent,  $\alpha_2$ ) fluctuation of heart rate (Fig.1). Crossover index was defined as  $\alpha_2/\alpha_1$ .

### 2.5. Approximate entropy.

The methodological details for computing approximate entropy,  $\text{ApEn}(m,r,N)$ , have been published elsewhere<sup>5,8,11,16-17</sup> and will be described briefly. In order to compute  $\text{ApEn}(m,r,N)$ , three input parameters should be fixed ( $m$  : the length of compared runs,  $r$  : the effective filter,  $N$  : the length of data points). Let each heartbeat interval data set be represented as  $x(i)$ .

$\text{ApEn}(m,r,N)$ =average over  $i$  of  $\log_e$ [conditional probability that  $|x(j+m)-x(i+m)| \leq r$ , given that  $|x(j+k)-x(i+k)| \leq r$  for  $k=0,1,\dots, m-1$ ]. (1)

From  $x(i)$ , vector sequences  $u(1)$  through  $u(N-m+1)$  are formed, defined by  $u(i)=[x(i),\dots,x(i+m-1)]$ . These vectors represent  $m$  consecutive  $x$  values, commencing with the  $i$ th point. Define the distance  $d[u(i), u(j)]$  between vector  $u(i)$  and  $u(j)$  as the maximum difference in their respective scalar components. Use the sequence  $u(1)$ ,  $u(2),\dots, u(N-m+1)$  to construct, for each  $i \leq N-m+1$ ,  $C_i^m(r)$  = (numbers of  $j \leq N-m+1$  such that  $d[u(i), u(j)] \leq r$ )/( $N-m+1$ ). Define

$$\Phi^m(r) = \sum_{i=1}^{N-m+1} \frac{\log_e C_i^m(r)}{N-m+1}$$

, and then define the approximate entropy  $\text{ApEn}(m,r,N)$

$$\begin{aligned} &= -[\Phi^{m+1}(r) - \Phi^m(r)] = -\left[ \sum_{i=1}^{N-m} \frac{\log_e C_i^{m+1}(r)}{N-m} - \sum_{i=1}^{N-m+1} \frac{\log_e C_i^m(r)}{N-m+1} \right] \\ &\cong -\sum_{i=1}^{N-m} \frac{\log_e C_i^{m+1}(r) - \log_e C_i^m(r)}{N-m} = (N \rightarrow \infty) - \sum_{i=1}^{N-m} \frac{\log_e [C_i^{m+1}(r) / C_i^m(r)]}{N-m} \end{aligned}$$

which equals the average over  $i$  of

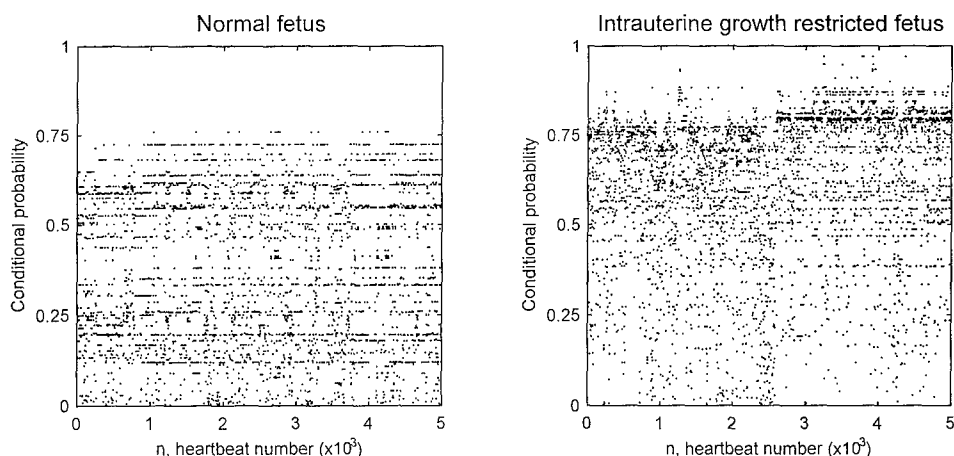
$$\log_e [C_i^{m+1}(r) / C_i^m(r)]$$

This last parenthetical expression is readily seen to be the conditional probability indicated in Eq. (1). For this study  $N = 5000$  points and the two parameters of standard deviation of each data set were  $m=2$  and  $r=20\%$  standard deviation of each data set. Fig. 2 plots all conditional probabilities over  $i=1,2,\dots,5000$ ,

$$C_i^{m+1}(r) / C_i^m(r)$$

of two heart rate data in an normal and an IUGR fetuses. Approximate entropy was the negative of the average logarithmic conditional probability, i.e.,

$$-\sum_{i=1}^{N-m} \frac{\log_e [C_i^{m+1}(r) / C_i^m(r)]}{N-m}$$



**Figure 2.** Plots of all conditional probabilities for calculating the approximate entropy of the two fetuses shown in Fig. 1, which is the negative of the average logarithmic conditional probabilities. The approximate entropy is much less in the growth restricted fetus than in the normal fetus (1.043 versus 0.532).

## 2.6. Statistical analysis.

All data are presented as mean  $\pm$  1 standard error of mean. To test the statistical difference in the involved parameters between the three groups, a procedure for general linear model (Statistical Analysis System 6.11) was used. When a significant statistical difference in the parameter among the three groups was identified, the difference between the two groups was compared with Duncan test. All analyses were performed using an alpha level of 0.05 as the criterion for statistical significance.

## 3. Results

In the IUGR group, the mean birth weight was  $2426 \text{ g} \pm 30$ , compared to  $3267 \text{ g} \pm 22$  in control group and  $3134 \text{ g} \pm 22$  in PIH group ( $p < 0.05$ ,  $p < 0.05$ ). The results of statistical, spectral and nonlinear analysis are summarized in table 1.

In the growth restricted group, the mean and the variance of heart rate were significantly higher compared to those of normal and PIH group. The frequency domain measures, low- and high-frequency power, were also significantly higher. However, the approximate entropy was significantly lower. Detrended fluctuation analysis revealed that all three groups showed apparent crossovers exhibited for the fractal scaling behavior of heart rate. The emergence of the crossover phenomena was due to a higher short-range fractal scaling exponent ( $\alpha_1$ ) compared to a long-range fractal scaling exponents ( $\alpha_2$ ) and, therefore, crossover index ( $\alpha_2/\alpha_1$ ) was far less than unity. The coefficient  $\alpha_1$  of the IUGR group was not significantly different from that of the normal group. However, the value of  $\alpha_2$  and  $\alpha_2/\alpha_1$  were significantly higher than those of the normal group. All indexes except the fractal measures in the PIH group were not significantly different to those of normal group.  $\alpha_1$  was significantly lower, and  $\alpha_2$  and  $\alpha_2/\alpha_1$  were significantly higher.

Table 1. Statistical, spectral, and nonlinear indexes of heart rate in normal and IUGR group for entire gestational periods.

Data are represented as mean  $\pm$  standard error of mean. IUGR: uncomplicated intrauterine growth restriction; PIH: pregnancy induced hypertension; bpm: beats per minute; \*  $<0.05$ , normal vs IUGR;  $\dagger p < 0.05$ , normal vs PIH;  $\ddagger p < 0.05$ , IUGR vs PIH.

	Normal group (n = 98)	IUGR group (n = 45)	PIH group (n = 46)
Mean (bpm)	141.7 $\pm$ 0.8	145.3 $\pm$ 1.4* $\ddagger$	142.4 $\pm$ 1.2
Variance (bpm <sup>2</sup> )	47.2 $\pm$ 3.5	85.6 $\pm$ 9.2* $\ddagger$	47.8 $\pm$ 6.4
Low-frequency power (msec <sup>2</sup> )	132.8 $\pm$ 9.5	204.3 $\pm$ 29.5* $\ddagger$	113.1 $\pm$ 1.0
High-frequency power (msec <sup>2</sup> )	23.8 $\pm$ 1.6	33.5 $\pm$ 5.0* $\ddagger$	22.9 $\pm$ 2.1
Approximate entropy	0.687 $\pm$ 0.017	0.578 $\pm$ 0.023* $\ddagger$	0.704 $\pm$ 0.028
Short-range scaling exponent ( $\alpha_1$ )	1.451 $\pm$ 0.107	1.419 $\pm$ 0.122	1.401 $\pm$ 0.015 $\ddagger$
Long-range scaling exponent ( $\alpha_2$ )	0.713 $\pm$ 0.022	0.970 $\pm$ 0.028*	0.915 $\pm$ 0.027 $\ddagger$
Crossover index ( $\alpha_2/\alpha_1$ )	0.492 $\pm$ 0.015	0.689 $\pm$ 0.023*	0.660 $\pm$ 0.022 $\ddagger$

#### 4. Discussion

By demonstrating the higher long-range fractal scaling exponent and crossover index in the IUGR and PIH group without any perinatal complication, and lower short-range fractal scaling exponent in the PIH group, it was uncovered that, although they were not severely compromised, their fractal heart rate behaviors were abnormal. By showing the decrease in approximate entropy in the IUGR group, it was also revealed that their irregular heart rate behavior was altered. In the PIH group, unlike in the IUGR group, only fractal measures could differentiate them from normal group. Furthermore, to differentiate the two groups from normal one, only the long-range fractal scale exponent or crossover index was useful.

The approximate entropy quantifies the irregularity in the time series by measuring randomness and nonlinearity in it.<sup>5,16-17</sup> Therefore, one distinguishing feature of the heart rate behaviors in the IUGR fetuses is that each heart rate tends to overshoot less or undershoot less (decreased nonlinearity) and to change less in random directions (decreased randomness).

The fractal scaling exponent measures absolute degree of temporal correlation and smoothness or roughness in heart rate fluctuation.<sup>4,8,12</sup>

Although the average value of short-range fractal scaling exponent in the PIH group was significantly higher, the values of all three groups were near 1.5. Therefore, on the short-range scale, their heart rate resembles smooth Brownian noise. The average value of the long-range fractal scaling exponent in the normal group was 0.713, which is near 0.5, and over long-range scale, the landscape of the heart rate time series resembles rough white noise, whereas the value in the IUGR and PIH group were near unity and their landscape resembles 1/f noise. Therefore, a distinguishing feature of their heart rate behavior from that of the normal group is that on the long-range scale the heart rate fluctuation is more timely correlated and smoother. The increased low-frequency oscillation evidenced by increased low-frequency power in the IUGR group (Table 1) and their possible increase in the duration of heart rate acceleration that occurred during fetal movement, fetuses might account for the increased long-range correlation and smoothness. However, this is not the case, since the long-range fractal scaling behavior operates at 80 - 1000 heartbeats, whose duration is beyond the period of the low-frequency and the period of the acceleration.

The abnormal fractal correlation behavior and/or decreased irregularity in the heart rate of the IUGR and PIH group may reflect the abnormalities in integrated complex cardiovascular control,<sup>8,18</sup> which may impair the fetuses' ability to adapt to external and internal perturbations and predispose the fetuses to perinatal mortality and morbidity.<sup>19-21</sup> This notion is supported by recent observations that either decreased long-range fractal scaling exponent<sup>7,8-10</sup> or approximate entropy<sup>11,22</sup> in heart rate dynamics was associated with patients with a variety of cardiovascular diseases.

In conclusion, by demonstrating abnormal fractal scaling measures and/or decreased approximate entropy in fetuses associated with IUGR and PIH and without any perinatal complications, we found that, although they are not severely compromised, their fractal and irregular heart rate behaviors were altered.

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